Trastuzumab biosimilar (BCD-022)

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General information

Description: Recombinant humanized IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2) that has been shown to inhibit the proliferation of HER2 overexpressing cancer cells.

INN: TRASTUZUMAB

Internal code: BCD-022

Dosage form: Powder for concentrate for solution for infusion

Indications:

- HER+ Breast cancer
- Gastric cancer

Manufacturer: The full manufacturing cycle and quality control are performed by JSC BIOCAD

BIOCAD trastuzumab in the world

Trastuzumab was first approved in the Russian Federation on 31 December 2015

- Supplied to and/or registered in **25+**[1] **countries**
- Approval process ongoing in > **20 countries**

Pharmacovigilance data without unexpected efficacy or safety reports on:

> 1 700 000 vials sold

> 120 000[2] patients treated

1 Number of countries, where the products are supplied to and/or registered, including temporary quarters and emergency tenders
2 Numbers on this page relevant as of October 2023. The calculation is based on the average recommended doses, average patient weight, and the approximate duration of therapy. The approximate trastuzumab dose for the treatment of one patient (regardless of the indication): 4836 mg

Summary on clinical studies of BCD-022

Type of Study	Phase	Primary Objective(s)	Study Design	Test Product(s); Regimen	Subjects	Duration of Treatment
PK and safety study PK	Phase I	Comparative study of PK and safety of BCD-022 and Herceptin® in combination with paclitaxel after a single-dose administration in subjects with HER2-positive metastatic breast cancer.	International multicenter comparative double-blind randomized study	BCD-022 or Herceptin® IV + paclitaxel IV	48 patients with HER2-positive mBC	Single administration (1 therapy cycle)
Efficacy, safety, IG and PK study	Phase III	Comparative study of the efficacy and safety of BCD-022 + paclitaxel or Herceptin® + paclitaxel as a first-line therapy of HER2-positive metastatic breast cancer.	International multicenter comparative double-blind randomized study	BCD-022 or Herceptin® IV + paclitaxel IV Q3W	225 patients with HER2-positive mBC	6 therapy cycles

Phase III study of trastuzumab biosimilar BCD-022

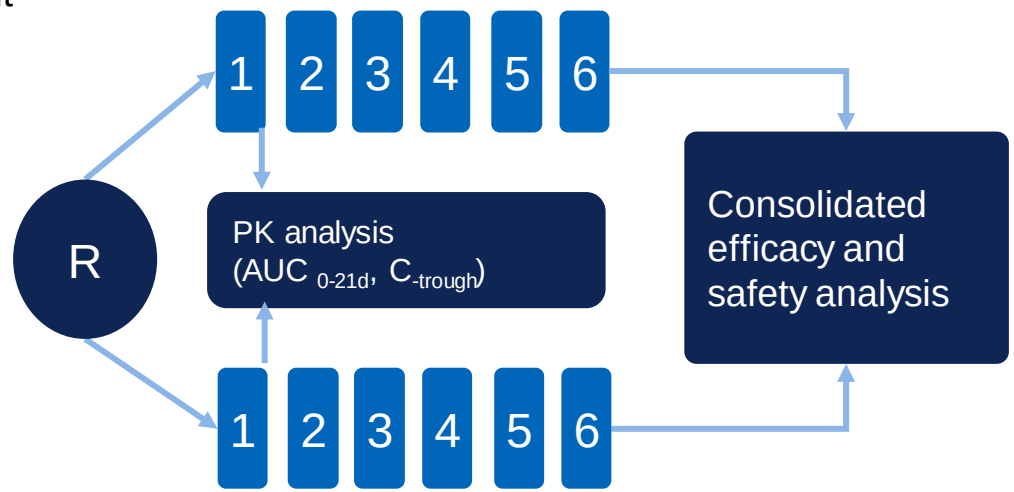
International multicenter double-blind randomized efficacy and safety study with PK assessment

Population: 225 females with HER2+ mBC, first-line treatment

Treatment duration: 6 cycles

Sites: 20 in Russian Federation, **11** international sites

Dates: 2012-2014



Study groups and treatment

Group 1 (BCD-022):
- paclitaxel 175 mg/m$_2$ every 3 weeks, on Day 1 (3 h infusion)
- **BCD-022** 8 mg/kg loading dose (1 cycle) → 6 mg/kg maintenance dose every 3 weeks on Day 1 (5 cycles)

Group 2 (reference trastuzumab*):
- paclitaxel 175 mg/m$_2$ every 3 weeks, on Day 1 (3 h infusion)
- **Reference trastuzumab** 8 mg/kg loading dose (1 cycle) → 6 mg/kg maintenance dose every 3 weeks on Day 1 (5 cycles)

Hypothesis

BCD-022 in combination with paclitaxel has equivalent efficacy and safety profile with original trastuzumab in combination with paclitaxel
in patients with HER2+ breast cancer

Reference trastuzumab is **Herceptin®**

Trastuzumab Phase III study:
Hypothesis and sample size calculation

- Study was planned using **two-sided equivalence hypothesis**
- Primary study endpoint — overall response rate
- Sample size was calculated using the following variables:
  - Equivalence margin $|\delta|$ = 0.2*
  - Significance level α=0.05
  - Power 80%

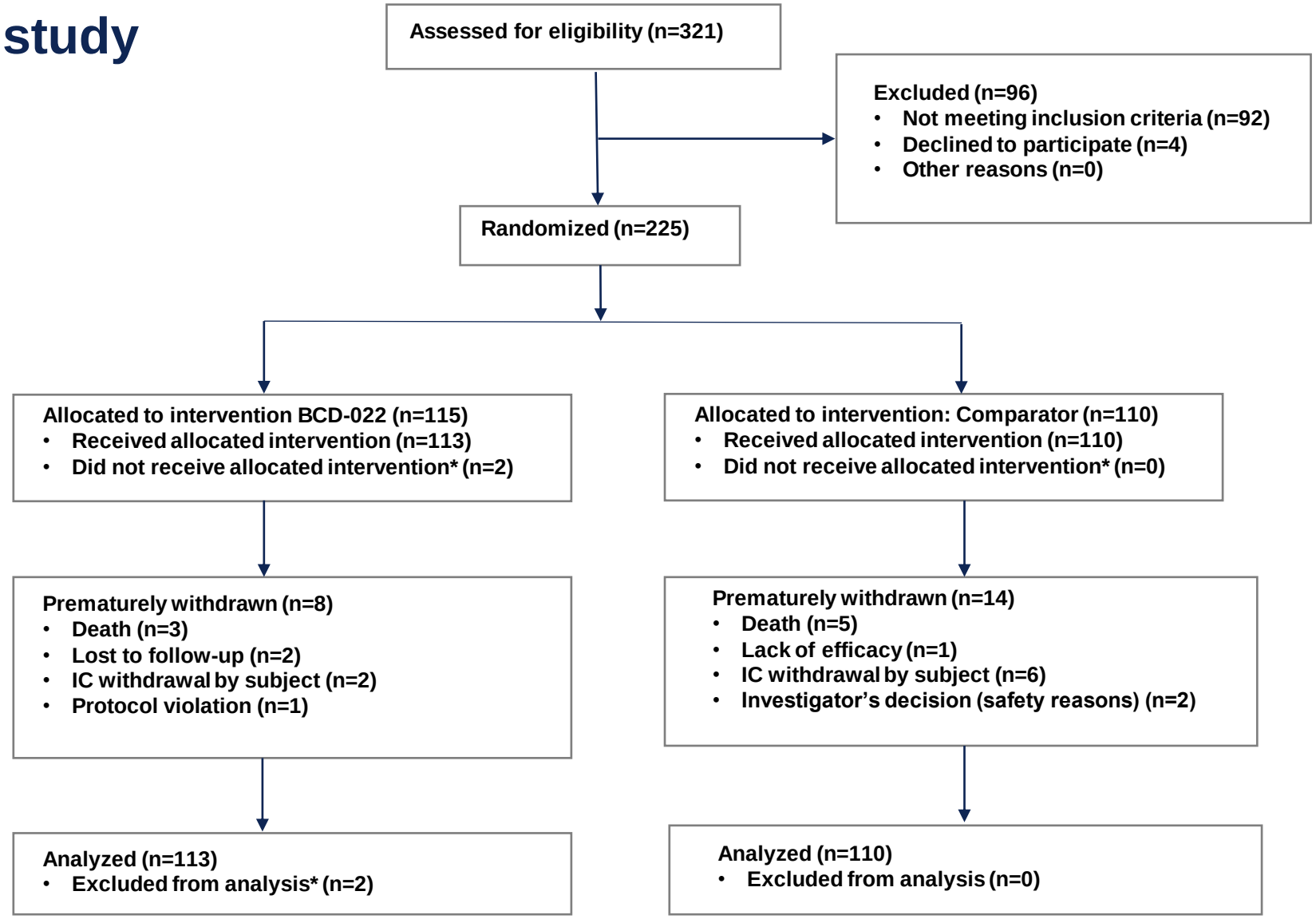
$$n = \frac{(z_\alpha + z_{\beta/2})^2}{(\delta - |\epsilon|)^2}\left[\frac{p_1(1-p_1)}{\kappa} + p_2(1-p_2)\right]$$

- Calculated total sample size n = 206

Clinical trial	Study therapy	Overall response rate (ORR)	Size of effect
Metastatic breast cancer (mBC)			
Slamon et al, 2001	trastuzumab + paclitaxel vs. paclitaxel	41% vs. 17%	24%
H0648g	trastuzumab + paclitaxel vs. paclitaxel	49% vs. 17%	32%
M77001	trastuzumab + docetaxel vs. docetaxel	61% vs. 34%	27%

* According to ICH E10 Guideline **the margin (delta)** value generally should not be higher than difference between active control and placebo (or absence of treatment).

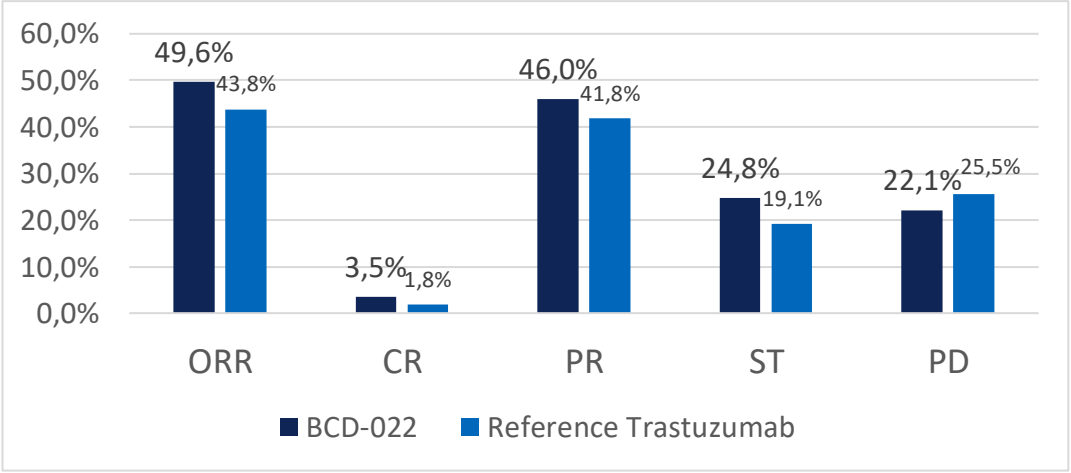
Trastuzumab Phase III international clinical study Subjects disposition



Efficacy analysis (ORR)

Primary efficacy endpoint assessment results

Parameter	BCD-022 (n = 113)		Reference trastuzumab (n = 110)		p*
	n	% (95% CI)	n	% (95% CI)	
Objective response rate (ORR)	56	49.6 (40.08- 59.07)	48	43.6 (34.31-53.41)	0.683
ORR difference	(-8.05) −19.89%				
Risk Ratio for ORR (90%CI)	1.1357 (0.8961, 1.4393)				



- **Biosimilarity of BCD-022 to reference trastuzumab was confirmed**
- The ORR (primary endpoint) showed no significant differences between the groups
- 95% CI for ORR difference (-8.05)−19.89% was within predetermined equivalence margin
- No differences between the groups in all other efficacy variables

Actual lower bound of CI is above -10%

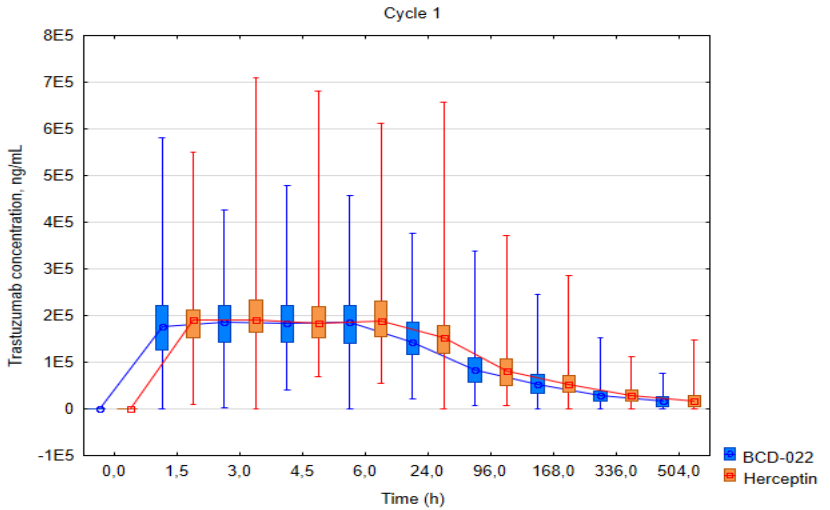
Pharmacokinetics (PK)

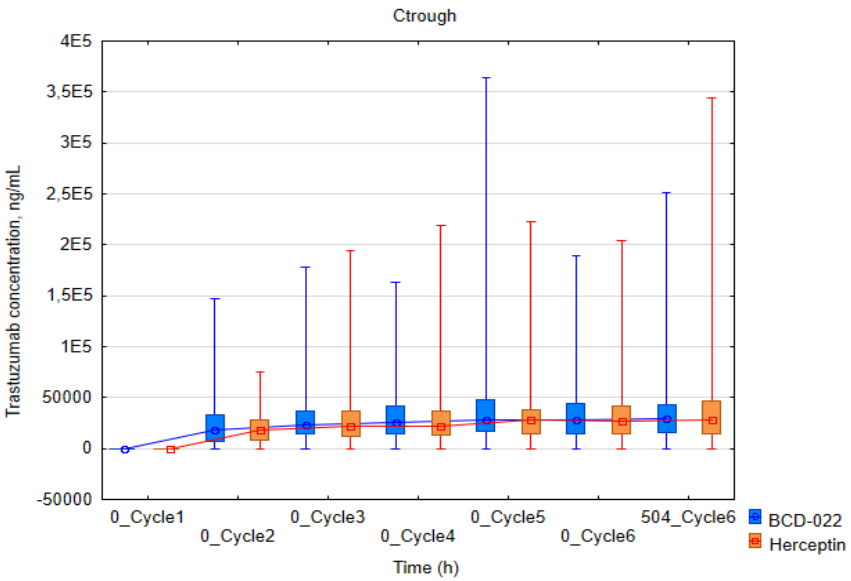
PK analysis after single administration (n=211)

Parameter	90% CI	90% CI equivalence intervals
$AUC_{(0-504)}$	87.66–109.01%	80% - 125%
C_{max}	90.89–106.03%	80% - 125%

Minimal serum concentration analysis C_{trough} (n=156)

The pharmacokinetics of BCD-022 was equivalent to that of reference trastuzumab





Safety

Parameter	BCD-022 (n = 113)		Reference trastuzumab (n = 110)		p-value*
	n	%	n	%	
Any AE/SAE	106	93.81	104	94.55	1.000
— **SAE**	8	7.08	13	11.82	0.326
— **Therapy-related SAE**	4	3.54	5	4.55	0.746
Courses postponed due to AE/SAE	4	3.54	5	4.55	0.746
Courses discontinued due to AE/SAE	0	0.00	1	0.91	0.493
Deaths**	3	2.65	5	4.55	0.495

*Two-tailed Fisher's exact test/Yates-corrected χ2 test;
**This tabulation does not include the lethal outcome in patient who was randomized but did not receive a single dose of the study drug

The AE profiles of BCD-022 and comparator were similar.

The rates of all AE (incl. SAE) did not significantly differ between the groups. Most AE were due to chemotherapy. The most common AE were hematological and non-hematological disorders and laboratory abnormalities

Immunogenicity

Parameter	BCD-022 (n = 113) n(%)	Reference trastuzumab (n = 110) n(%)	p-value*
Binding antibodies (Screening)	8 (7.08)	15 (13.46)	0.165[2]
Binding antibodies (throughout the study)	4 (3.54)	3 (2.73)	1.000[1]
Neutralizing antibodies (Screening and/or throughout the study)	3 (2.65)	4 (3.64)	1.000[2]

[1] - Pearson's chi-squared test, [2] - Fisher's exact test;

- There was no notable influence of presence of ADA or NAB on AUC or ORR
- C-through values at 6th Cycle were higher in ADA(+) vs. ADA(-) for both BCD-022 and reference trastuzumab groups
- ADA did not reduce the levels of trastuzumab in the blood of patients.
- No negative influence of the presence of ADA or NAB on PFS and OS

Trastuzumab biosimilar BCD-022 phase 3 study conclusions

- The efficacy, safety and pharmacokinetics analysis confirmed equivalence between BCD-022 and reference trastuzumab arms.
- The difference in ORR between the group 1 and group 2 was -0.13% with 95% CI (-19.83% — 13.35%) ($p = 0.862$, Yates-corrected X^2 test). The lower limit of the estimated 95% CI (-19.83%) exceeded the pre-specified non-inferiority margin therefore, the hypothesis that BCD-022 is non-inferior to reference trastuzumab was confirmed.
- The safety analysis has shown that BCD-022 and reference trastuzumab have similar safety and tolerability characteristics and similar immunogenicity profiles.
- The obtained data demonstrates the therapeutic equivalence of the BCD-022 and the reference trastuzumab.

Trastuzumab biosimilar BCD-022 phase III study publication in BMC Cancer journal

Alexeev *et al. BMC Cancer* (2020) 20:783
https://doi.org/10.1186/s12885-020-07247-9

BMC Cancer

RESEARCH ARTICLE Open Access

Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-022 with reference trastuzumab

Sergey M. Alexeev[1], Andrey V. Khorinko[2], Guzel Z. Mukhametshina[3], Konstantin G. Shelepen[4], Olga N. Burdaeva[5], Sergey A. Kulik[6], Chiradoni Thugappa Satheesh[7], Kirti Srivastava[8], Mummaneni Vikranth[9], Fedor Kryukov[10*], Anastasia N. Paltusova[10], Mariya S. Shustova[10] and Roman A. Ivanov[10]

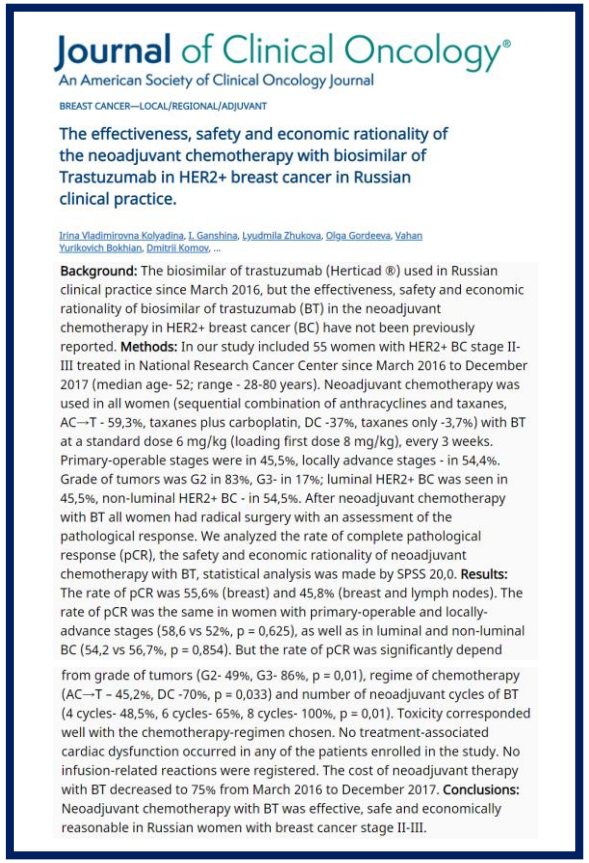
Reference:
Alexeev SM, Khorinko AV, Mukhametshina GZ, Shelepen KG, Burdaeva ON, Kulik SA, Satheesh CT, Srivastava K, Vikranth M, Kryukov F, Paltusova AN, Shustova MS, Ivanov RA. Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-022 with reference trastuzumab. BMC Cancer. 2020 Aug 20;20(1):783. doi: 10.1186/s12885-020-07247-9. PMID: 32819305; PMCID: PMC7439710.
https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-07247-9

BIOCAD trastuzumab biosimilar in real world clinical practice

Results of routine clinical practice use of trastuzumab biosimilar BCD-022 were reported on ASCO 2018

http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e12656

https://www.centerforbiosimilars.com/conferences/asco-2018/



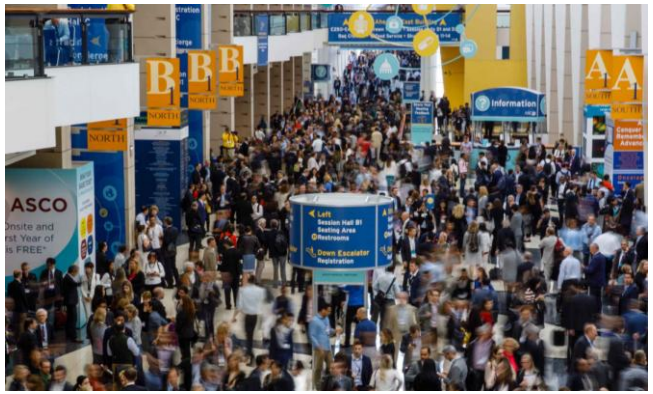
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

BREAST CANCER—LOCAL/REGIONAL/ADJUVANT

The effectiveness, safety and economic rationality of the neoadjuvant chemotherapy with biosimilar of Trastuzumab in HER2+ breast cancer in Russian clinical practice.

Irina Vladimirovna Kolyadina, I. Ganshina, Lyudmila Zhukova, Olga Gordeeva, Vahan Yurikovich Bokhian, Dmitrii Komov, ...

Background: The biosimilar of trastuzumab (Herticad ®) used in Russian clinical practice since March 2016, but the effectiveness, safety and economic rationality of biosimilar of trastuzumab (BT) in the neoadjuvant chemotherapy in HER2+ breast cancer (BC) have not been previously reported. **Methods:** In our study included 55 women with HER2+ BC stage II-III treated in National Research Cancer Center since March 2016 to December 2017 (median age- 52; range - 28-80 years). Neoadjuvant chemotherapy was used in all women (sequential combination of anthracyclines and taxanes, AC→T - 59,3%, taxanes plus carboplatin, DC -37%, taxanes only -3,7%) with BT at a standard dose 6 mg/kg (loading first dose 8 mg/kg), every 3 weeks. Primary-operable stages were in 45,5%, locally advance stages - in 54,4%. Grade of tumors was G2 in 83%, G3- in 17%; luminal HER2+ BC was seen in 45,5%, non-luminal HER2+ BC - in 54,5%. After neoadjuvant chemotherapy with BT all women had radical surgery with an assessment of the pathological response. We analyzed the rate of complete pathological response (pCR), the safety and economic rationality of neoadjuvant chemotherapy with BT, statistical analysis was made by SPSS 20,0. **Results:** The rate of pCR was 55,6% (breast) and 45,8% (breast and lymph nodes). The rate of pCR was the same in women with primary-operable and locally-advance stages (58,6 vs 52%, p = 0,625), as well as in luminal and non-luminal BC (54,2 vs 56,7%, p = 0,854). But the rate of pCR was significantly depend from grade of tumors (G2- 49%, G3- 86%, p = 0,01), regime of chemotherapy (AC→T – 45,2%, DC -70%, p = 0,033) and number of neoadjuvant cycles of BT (4 cycles- 48,5%, 6 cycles- 65%, 8 cycles- 100%, p = 0,01). Toxicity corresponded well with the chemotherapy-regimen chosen. No treatment-associated cardiac dysfunction occurred in any of the patients enrolled in the study. No infusion-related reactions were registered. The cost of neoadjuvant therapy with BT decreased to 75% from March 2016 to December 2017. **Conclusions:** Neoadjuvant chemotherapy with BT was effective, safe and economically reasonable in Russian women with breast cancer stage II-III.



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Researchers Report Findings on Three Biosimilar Trastuzumab Products

During the 2018 American Society of Clinical Oncology's Annual Meeting, researchers presented findings on 3 biosimilar trastuzumab products: Samsung Bioepis' SB3, Agmen's ABP 980, and Biocad's Herticad.

Kelly Davio
June 04, 2018

Biocad's Herticad reduced the cost of trastuzumab therapy by 75%

Biocad's Herticad, which is approved for use in Russia, has been available since 2016, and new research reports on the effectiveness, safety, and economics of using the biosimilar in clinical practice.[3]

Researchers conducted a study that included 55 women with stage 2 or stage 3 HER2-positve breast cancer who were treated at Russia's National Research Cancer Center from March 2016 to December 2017. All patients received neoadjuvant chemotherapy together with the biosimilar trastuzumab, after which all patients had surgery with an assessment of pCR.

The rate of pCR was 55.6% in the breast and 45.8% in the breast and lymph nodes, and was similar in patients with primary-operable and locally-advanced disease. There were no reports of treatment-associated cardiac dysfunction in any of the patients, nor were there any infusion-related reactions.

The cost to provide neoadjuvant therapy with trastuzumab decreased 75% during the study period by using the biosimilar, and the researchers report that the biosimilar provides an economically reasonable option that is both safe and effective.

References

1. Pivot X, Bondarenko I, Nowecki Z, et al. Additional one-year follow-up study to evaluate safety and survival in patients who have completed neoadjuvant-adjuvant treatment with SB3 (trastuzumab biosimilar) or reference trastuzumab in HER2-positive early or locally advanced breast cancer. *J Clin Oncol.* 2018;36 (suppl; Abstract e12631).

2. Kolberg HC, Tomasevic Z, Demetriou G, et al. Efficacy analyses of central laboratory pCR results from the LILAC study comparing the biosimilar ABP 980 and trastuzumab. *J Clin Oncol.* 2018;36 (suppl; Abstract 583).

3. Kolyadina IV, Ganshina I, Zhukova L, et al. The effectiveness, safety and economic rationality of the neoadjuvant chemotherapy with biosimilar of trastuzumab in HER2+ breast cancer in Russian clinical practice. *J Clin Oncol.* 2018;36 (suppl; Abstract e12656).

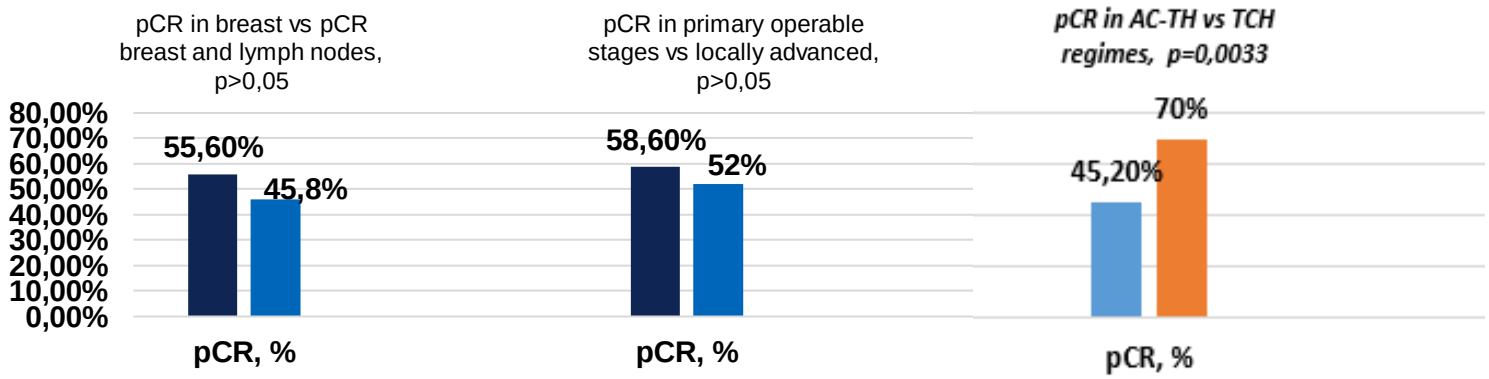
Neoadjuvant chemotherapy with Herticad® in real world clinical practice

- **The study included 55 women** with HER2+ BC stage II-III treated in N.N.Blokhin Russian Cancer Research Center (Moscow) from March 2016 to December 2017
- Median age 52y; range - 28-80 years.
- T1-3N0-1 - 45,5%, locally advanced stages (T4; N2-3) 54,4% patients
- Luminal HER2+ BC was seen in 45,5%, non-luminal - 54,5% patients.

Neoadjuvant chemotherapy included Trastuzumab biosimilar in all women with:

- 4AC→12 weekly paclitaxel - 59,3% pts,
- 6 x docetaxel plus carboplatin - 37% pts,
- taxanes only - 3,7% pts

The results of our study



The study has demonstrated effectiveness and safety of trastuzumab biosimilar in real-world practice